Cell-fate determination by ubiquitin-dependent regulation of translation.

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Public Summary:
This work describes the molecular origin of the craniofacial disease Treacher Collins Syndrome, thus providing a path for future therapeutic developments. Using hESCs as our model, we identified a cellular enzyme that can re-tool the protein synthesis machinery in a way that allows a particular cell type, neural crest cells, to emerge. Cranial neural crest cells develop into chondrocytes, which in turn secrete a collagen matrix that serves as a blueprint for facial bone formation. Mutations in the key substrate of our enzyme prevent neural crest formation, and consequently, disrupt the generation of many facial bone structures.

Scientific Abstract:
Metazoan development depends on the accurate execution of differentiation programs that allow pluripotent stem cells to adopt specific fates. Differentiation requires changes to chromatin architecture and transcriptional networks, yet whether other regulatory events support cell-fate determination is less well understood. Here we identify the ubiquitin ligase CUL3 in complex with its vertebrate-specific substrate adaptor KBTBD8 (CUL3(KBTBD8)) as an essential regulator of human and Xenopus tropicalis neural crest specification. CUL3(KBTBD8) monoubiquitylates NOLC1 and its paralogue TCOF1, the mutation of which underlies the neurocristopathy Treacher Collins syndrome. Ubiquitylation drives formation of a TCOF1-NOLC1 platform that connects RNA polymerase I with ribosome modification enzymes and remodels the translational program of differentiating cells in favour of neural crest specification. We conclude that ubiquitin-dependent regulation of translation is an important feature of cell-fate determination.